

POSTER PRESENTATION

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CITN11-02 interim trial results: subcutaneous administration of recombinant human IL-15 (rhIL-15) is associated with robust expansion of peripheral blood CD56+ NK cells

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Background

IL-15 activates and induces the proliferation of CD8+ T cells and NK cells. The Cancer Immunotherapy Trials Network (CITN) is conducting a Phase I, open-label, dose-escalation study of subcutaneous (SQ) rhIL-15 in advanced melanoma, renal cell, non-small cell lung and squamous cell head and neck carcinoma patients. The primary objective is to determine the maximum tolerated dose; secondary objectives include evaluation of immunological activity defined by increases in circulating lymphocytes.

Methods

Each cycle consists of 5 daily SQ injections of rhIL15 (E.coli-derived, NCI) administered Monday-Friday for two weeks, followed by 2 weeks observation. The absolute lymphocyte count is evaluated daily during the 10 days of SQ injection and whole blood flow cytometric analysis of T and NK cell numbers is conducted on Days 1 and 11 of each cycle.

Results

Three patients have been enrolled in each of the 0.25, 0.5, 1.0 and 2.0 mcg/kg/dose cohorts (n = 12). Ten patients have completed 2 or more cycles and two have completed one. Only one serious adverse event, grade 2 pancreatitis, was observed in a metastatic melanoma patient and began 3 days after completing Cycle 1 treatment at 2.0 mcg/kg.

Flow cytometric data indicate a consistent increase in the frequency of CD3-CD56+ NK cell numbers at Day 11 compared to Day 1 of Cycle 1 (mean 3.6-fold increase, range 0.7-8.1). Notably, the subpopulation of CD56^{bright} NK cells increased 6.7-fold (mean, range 1.8-17.9). Increases in CD56+ and CD56^{bright} NK cell frequencies were less pronounced in Cycle 2 (mean fold-increase = 1.6 and 2.9, respectively) and in subsequent cycles. The percentage of CD56+ NK cells among CD45+ cells was higher on Day 11 (mean = 20, range 9-32%) compared to Day 1 of Cycle 1 (mean = 8, range 3-22%). Two patients demonstrated remarkably high percentages of CD56+ NK cells peaking at 42-43% of CD45+ cells. By marked contrast, the frequency of CD8+ T cells was largely unchanged during Cycle 1 (mean fold-increase = 1.2, range 0.5-2.9) and subsequent cycles.

Conclusion

SQ rhIL-15 was very well tolerated through the 2 mcg/kg/dose, associated with an increase in CD56+ NK cells, and a substantial expansion in the CD56^{bright} NK cell subpopulation. The effect on peripheral blood T cells was surprisingly minimal. The 2 mcg/kg/dose cohort will be expanded to six patients before dose escalation proceeds. After defining the optimal dosing regimen, combinations with appropriate monoclonal antibodies will be of interest.

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